Difference in Distribution of Methionine and FDG in Tumor Tissues in Vivo

III. 11. Difference in Distribution of Methionine and FDG in Tumor Tissues in Vivo

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Introduction

2-Deoxy-2-[^{18}F]fluoro-D-glucose (^{18}F-FDG) and L-[methyl-^{11}C]methionine (^{11}C-Met) are used for cancer imaging by positron emission tomography (PET). In this study, we report ^{18}F-FDG and^{14}C-Met uptake, instead of ^{11}C-Met for experiments, by each of various cellular elements in mouse malignant tumor models of different growth rates by microautoradiography. Possible different roles of these tracers in cancer imaging were discussed.

Materials and Methods

The study protocol with animals was approved by the Laboratory Animal Care and Use Committee of Tohoku University.

Ten week-old C3H/He female mice were subcutaneously injected with a 0.1-ml suspension of 10^7 syngeneic FM3A mammary carcinoma cells and 10^6 syngeneic MH134 hepatoma cells, respectively, into the left and right thighs. Tracer experiments were performed 10 days after transplantation[1].

Ten mice bearing both FM3A and MH134 tumors were injected intravenously with 37 MBq of ^{18}F-FDG or 185 kBq of ^{14}C-Met in 0.2 ml of saline and killed 1 hr later. The tumors were quickly removed, cut into frozen sections, then 3.5-μm thick sections were processed for microautoradiography[1,2]. After exposure for 4 hr (^{18}F-FDG) and 20 days (^{14}C-Met), the sections were developed, fixed and stained with hematoxylin and eosin. The silver grains were counted in various tumor regions under a transmitted light brightfield microscope using a micrometer.

Results

The silver grain density of ^{18}F-FDG and ^{14}C-Met in various cellular elements within MH134 and FM3A tumor tissues was studied by microautoradiography. Tumor tissue

components of interest with silver grain densities were as follows: (1) viable tumor cells; (2) tumor-associated macrophages; (3) young granulation tissue; (4) extensive necrosis; (5) focal necrotic cell debris; and (6) necrobiotic cells.

In ^{14}C-Met uptake analysis in both MH134 and FM3A, the viable tumor cells showed the highest uptake. MH134 tumor cells was 1.4-folds higher than FM3A tumor cells. Macrophages and young granulation tissues showed much lower uptake than viable tumor cells. Majority of ^{14}C-Met uptake was occurred in viable tumor cells. In the global observation of ^{14}C-Met uptake by the tomor tissues, the uptake by viable tomor cells was high and that by the other coomponents was markedly low.

In ^{18}F-FDG uptake analysis in both MH134 and FM3A, tumor-associated macrophages showed the highest uptake followed by necrobiotic cells and young granulation tissue. The uptake by viable tumor cells was markedly lower than the uptakes by above cellular components. The uptakes by focal cell debris and extensive necrosis were the lowest. ^{18}F-FDG uptake by cellular components within tumor tissue was distributed to the full range. MH134 showed higher uptake than FM3A.

Discussion

^{18}F-FDG and ^{14}C-Met showed obviously different uptake profile in the tumor tissues. In the ^{14}C-Met uptake study, only the uptake in the viable tumor cells was high and the uptakes by the other components were relatively low with a similar range. ^{14}C-Met is a tracer which reflects the extension and viability of viable tumor cells. ^{14}C-Met may be suitable for the treatment evaluation. Because the intratumoral responses by the treatments, such as the respilatory burst of activated macrophages[3] and the increments of necrobiotic cells, may not affect the ^{14}C-Met uptake meaningfully.

In contrast, ^{18}F-FDG uptake was distributed to the full range. As described previously[2], ^{18}F-FDG uptake in the tumor is accentuated by the tumor-associated macrophages and young granulation tissues. ^{18}F-FDG uptake correlates to DNA synthesis activity, and DNA synthesis activity correlates to in vivo growth rates[4]. The uptake by macrophages are higher in the highly proliferative tumors[1]. Development of multifocal necrosis suggests high-grade of malignancy of the tumors[5]. ^{18}F-FDG seems to be a tracer which reflects the tumor-host immune system reaction. The reaction may be favorable for FDG-PET studies for grading because highly proliferative tumors show higher ^{18}F-FDG uptake by whole tumor. ^{18}F-FDG may suit for pretreatment diagnosis. Treatment evaluation using ^{18}F-FDG needs attention because the increments of activated macrophages and necrobiotic cells may induce high ^{18}F-FDG uptake even though no tumor cells are viable.

The tracer should be selected by the aim of study because each tracer has different uptake characteristics.

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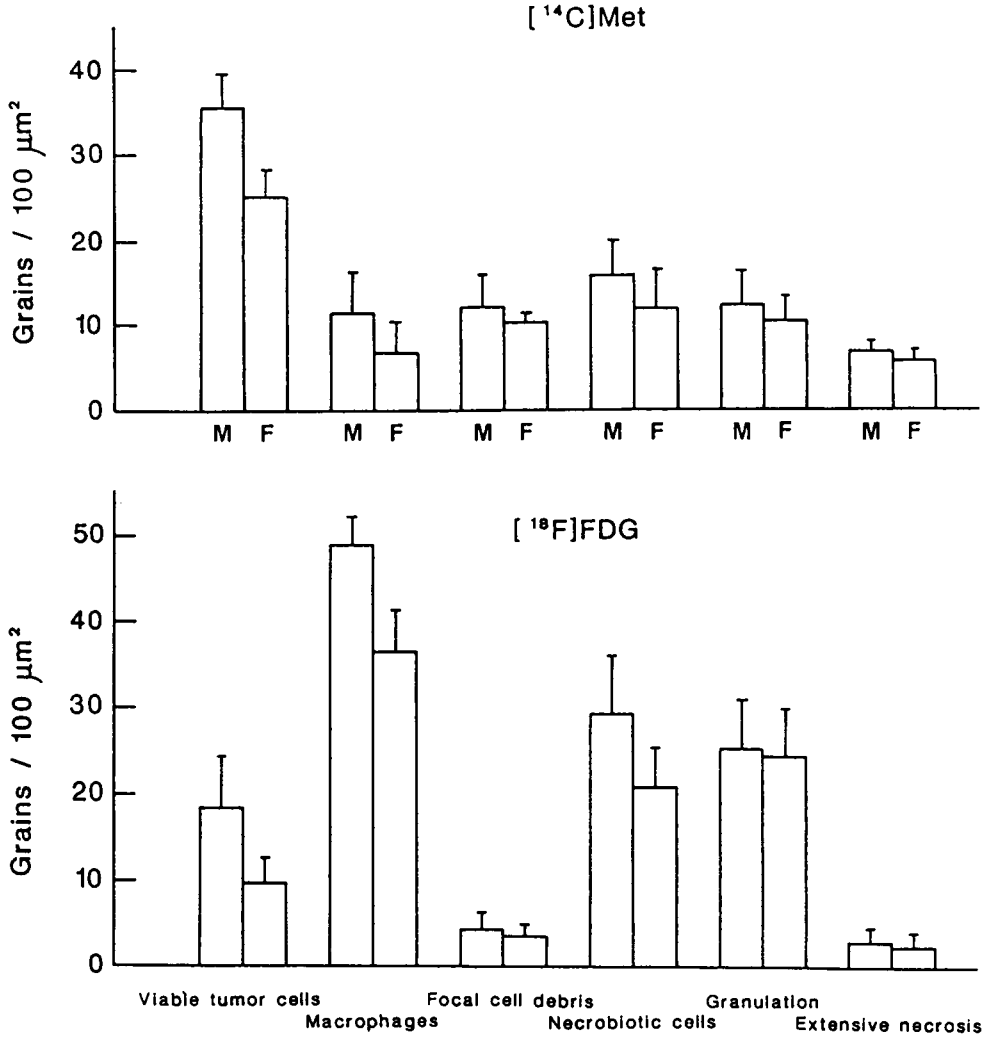

Fig. 1. Uptake of ^{14}C-Met and ^{18}F-FDG by cellular components within MH134 and FM3A tumor tissues. The uptake was represented by the number of grains per unit area. M: MH134 tumor tissue; F: FM3A tumor tissue.